Journal of Taibah University Medical Sciences (2012) 7(1), 35–40

Taibah University

Journal of Taibah University Medical Sciences

www.jtaibahumedsc.net
www.sciencedirect.com

Clinical Study

Nutritional rickets in Almadinah Almunawwarah: Presentation and associated factors

Abdelwahab T.H. Elhassan Elidrissy, FRCPE, DCH, FRCPCH [a,*], Abdallah Mohmmed Sandokji [a], Mohmmed Saed Faleh Al-Magamsi, CABP [b], Zakaria Mohamed Al-Hawsawi, CABP [b], Abdelrahman Saud Al-Hujaili [b], Naji Hamoud Babiker, CABP [b], Ahmed Mohamed Yousif, DCH [b]

[a] *Department of Pediatrics, College of Medicine, Taibah University, Almadinah Almunawwarah, Saudi Arabia*
[b] *Department of Pediatrics, Maternity and Children's Hospital, Almadinah Almunawwarah, Saudi Arabia*

Received 2 February 2012; revised 30 April 2012; accepted 22 May 2012

KEYWORDS

25OHD;
Breastfeeding;
Vitamin D deficiency

Abstract *Objectives:* To study vitamin D deficiency rickets and associated factors in the Almadinah Almunawwarah region, where this problem has not been studied previously, despite reports from other parts of Kingdom of Saudi Arabia.

Methods: We conducted a prospective hospital-based study of cases of rickets or hypocalcaemia seen in the outpatient clinic or admitted to the main referral hospital between October 2008 and March 2009. Socioeconomic, clinical and biochemical data were collected and analyzed to determine the factors associated with rickets include environmental, nutritional and maternal in Almadinah Almunawwarah region.

Results: The presenting features of the 136 cases of rickets seen were diarrhoea and vomiting or cough and fever in 48, convulsions in 11 infants (8.1% of the total and 33.3% of those aged less than 1 year), bow legs in 78, delayed dentition in 33, delayed standing in 38, hypotonia in 25, abnormal gait in 54 and sweating in 33. The factors associated with rickets were multiple.

Conclusion: Rickets is prevalent in the Medina region. The main factor associated with its prevalence was environmental and cultural avoidance of exposure to the sun, which shines all the year round. As rickets is a preventable disease, vitamin D supplementation should be given. All breastfed

* Corresponding author. Address: Professor of Paediatrics, Department of Pediatrics, College of Medicine, Taibah University, 30001 Almadinah Almunawwarah, Saudi Arabia. Tel.: +966 4 8460008; fax: +966 4 8447884.
E-mail address: elidrissytazy@hotmail.com (A.T.H.E. Elidrissy).

Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jtumed.2012.07.002

infants should be given the recommended 400 IU daily, and the mothers during pregnancy and lactation should be supplemented with 1000 units of vitamin D3, to prevent rickets in their infants and avoid diseases in themselves.

Introduction

Since we first described rickets in Kingdom of Saudi Arabia, a country with a high sun factor, in 1980, reports have been made from other parts of the country but not from the north-west (Almadinah Almunawwarah Region).[1–5] We therefore decided to study the factors associated with rickets and its presentation in Almadinah Almunawwarah to complete the analysis. The study was conducted in the Maternity and Children's Hospital Almadinah Almunawarrah, a 400-bed hospital and the main pediatric referral hospital in the region. As we found rickets in infants at a mean age of 10 months in the Riyadh region, we proposed that maternal vitamin D deficiency is a major factor in the pathogenesis of rickets in breastfed infants. We confirmed this hypothesis by reporting vitamin D deficiency in the mothers of rachitic infants.[6] Further, we found that the concentration of 25-hydroxyvitamin D (25OHD) in the cord blood of newborns and their mothers was low, although cord blood calcium was higher than that of the mothers.[7–10] Another study in Riyadh confirmed our findings, showing a drop in calcium level in the infants of vitamin D-deficient mothers on the seventh day of life.[11] The aim of the study reported here was to investigate the factors associated with vitamin D deficiency in all regions of Kingdom of Saudi Arabia.

Materials and methods

All 136 infants with a diagnosis of clinical rickets seen at the clinic or admitted to hospital in the 6-month period between October 2008 and March 2009, with hypocalcaemic convulsions or clinical features of rickets were included in the study. A form eliciting socioeconomic and clinical data was filled in for each patient. Blood samples for biochemical and haematological testing were collected as per the hospital policy. Further blood samples for determining 25OHD levels were collected randomly from both mothers and infants and stored at −70 °C for later analysis. Radiology of the right wrist was conducted for each person, and other sites were examined radiologically if needed. The cases were divided into three groups: infants below 1 year of age, children over 1 year and below 2 years and children over 2 years of age. Further, all cases diagnosed clinically as rickets or hypocalcaemia were divided into active or healed rickets according to radiological evidence of activity or healing of the wrist by the Thatcher criteria.[12] Nutritional status was assessed by weight for age and plotted on the Saudi growth chart.[13]

Results

Socio –economic data

The 136 cases of rickets and hypocalcaemia comprised 78 (57.3%) boys and 58 (42.9%) girls, of whom 122 (89%) were Saudis and 14 (11%) were non-Saudis. Consanguinity was found for 56 infants of first-degree cousins (41.1%) and 23 infants of second-degree cousins (16.9%); the parents of 11 further infants were more distantly related (8.1%), and the parents of 43 (31.6%) were not related. Ethnic grouping showed that 125 (91.9%) were of Arabic origin and 9 (6.6%) of African origin. The review of maternal education showed that the mothers of 34 infants (25%) had higher education,

Table 1: Presentation in active rickets at presentation according to age groups: A below one year, B between one and two years, and C above two years of age.

	Symptom or sign	Age <1 $N = 27$	%	Age 1–2 $N = 40$	%	Age >2 $N = 19$	%	Total $N = 86$	%
Non-specific Causes of presentation of rachitic cases	Convulsions	9	33.3	0	0.0	0	0.0	9	12.8
	Diarrhea and vomiting	5	18.5	6	15.0	0	0.0	11	8.1
	Fever	5	18.5	6	15.0	1	53.0	12	14
	Unwell	2	7.4	2	5.0	3	15.8	7	8.1
	Cough	3	11.1	6	15.0	0	0.0	9	10.5
	Others	6	22.2	5	12.5	5	26.3	16	18.6
Rickets related features at presentation	Bow legs	0	0.0	21	52.5	12	63.2	24	28
	Delay dentition	7	25.9	13	32.5	1	5.3	21	24.4
	Delay standing	5	18.5	19	47.5	3	15.8	27	31.3
Signs of rickets	Hypotonia	9	33.3	9	22.5	1	5.3	19	22.1
	Abnormal gait	0	0.0	21	52.5	14	73.7	35	40.7
	Sweating	6	22.2	14	35.5	3	15.8	23	26.7
	Craniotabes	6	22.2	0	0.0	0	0.0	6	0.7
	Frontal bossing	24	88.8	35	87.5	14	73.7	73	84.9
	Wide wrist	25	92.6	35	87.5	17	89.5	77	89.5
	Harrison sulcus	11	40.7	15	37.5	4	21.1	30	34.9
	Costo-chondral beading	12	44.4	25	62.5	7	36.8	44	51.2
	Bow legs	11	40.7	31	77.5	12	63.2	54	62.8

63 (44%) were graduates of intermediate or secondary schools, 17 (12.5%) were able to read and write and 21 (15.4%) were illiterate. The father's monthly income was below 2000 Riyals in 29 (21.9%) cases, 2000–4000 Riyals in 39 (29.5%) cases and above 4000 Riyals in 64 (48.5%) cases. The type of housing was a flat for the parents of 95 (70%) infants, while most of the rest lived in traditional houses. The infants and mothers were not exposed to the sun in 88 (64.7%) cases, and 116 (85%) infants were traditionally wrapped up. As regards feeding history, 94% were breastfed and 6% were not.

Clinical features

The clinical features of all infants and children for whom the parents sought medical advice are shown in Table 1 according to age group. Diarrhea and vomiting or cough and fever were recorded in 48 cases (35%). The cause of hospitalization was convulsions in 11 (8.1%) cases, and these represented 33.3% of infants under 1 year of age. Bow legs were found in 78 (57.4%), delayed dentition in 33 (24.3%), delayed standing in 38 (27.9%), hypotonia in 25 (18.4%), abnormal gait in 54 (39.9%) and sweating in 33 (24.3%). Clinical examination revealed craniotabes in 9 (6.6%), frontal bossing in 110 (80.9%) and delayed dentition in 38 (27.9%). Wide wrist was noted in 114 cases (83.3%) and costo-chondral beading in 54 (39.7%). Bow legs were found in 90 (66.2%) and waddling gait in 68 (50%). Hypotonia was noted in 34 (25%) and bone fracture in 2 (1.5%). Active rickets was diagnosed in 86 (63%) children and healed rickets in 50 (37%). The mean age was 17.0 months for those with active rickets and 23.9 months for those with healed rickets, the difference being significant ($P = 0.0232$). The meean weight was 8.5 kg for children with active rickets and 11.4 kg for those with healed rickets, with a highly significant difference ($P = 0.0004$). The mean height was 70 cm for children with active rickets and 80 cm for those with healed rickets, which was also significant ($P = 0.0001$). The mean head circumference was 46 cm in active rickets and 47.2 cm in healed rickets ($P = 0.1404$).

The mean chest circumference was 44.1 cm in active rickets and 46.8 cm in healed rickets, with a significant P value of 0.0024.

As the age of the child appeared to play a role in presenting symptoms and signs, we compared the symptoms and signs of active and healed rickets in the three age groups (Table 2). The clinical features were divided into three groups: general clinical symptoms not specifically related to rickets, classical clinical symptoms of rickets and classical signs of rickets. The symptoms not due directly to rickets were diarrhoea and vomiting, coughing, fever, convulsions and feeling unwell. The classical features of rickets included delayed dentition and bow legs.

Biochemical results

The biochemical results for children with active and healed rickets are shown in Table 3. Calcium, phosphorus and 25-hydroxycholecalciferol were significantly lower in active rickets than in healed rickets, whereas alkaline phosphatase and parathormone were significantly higher in active rickets. The mean parathormone level was 199.8 in active rickets and 60.8 in healed rickets, with a highly significant P value of 0.002. The alkaline phosphatase levels in active and healed rickets, with 500 IU taken as the cut-off point for normal, are shown in Figure 1.

Discussion

This hospital-based study, although it cannot be considered an epidemiological study, showed that rickets is prevalent in the Almadinah Almunawwarah area to a degree that it is a major

Table 2: Comparison of clinical feature in active and healed rickets in the study group (136).

%	Healed	%	Active	Symptoms	
10.0	5	13.95	12	Diarrhea and vomiting	General causes of bringing child to hospital
14.0	7	10.5	9	Cough	
8.0	4	14.0	12	Fever	
2.0	1	10.5	9	Convulsions	
12.0	6	8.1	7	Unwell	
72.0	36	48.8	42	Bowing of legs	Causes of referral related to rickets
24.0	12	24.4	21	Delay dentition	
22.0	11	31.4	27	Delay standing	
12.0	6	22.1	19	Hypotonia	
44.0	22	37.2	32	Abnormal Gait	
20.0	10	26.7	23	Sweating	
26.0	13	25.6	22	Others	

Table 3: Biochemical findings in infants with active and healed rickets.

Rickets status	Age in months	25OHD ng/ml >25 normal	PTH (9–65 pg/ml)	Calcium mmol/L 2–2.5	Phosphrous mmol/L 0.87–1.45	Alkaline phosphtase IU/L 50–135 Ad
Active	17	12.39	199.9	2.04	1.1	1207
Healed	23.9	52.6	60.8	2.3	1.8	344
P		<0.0001	0.002	0.0001	<0.0001	<0.0001

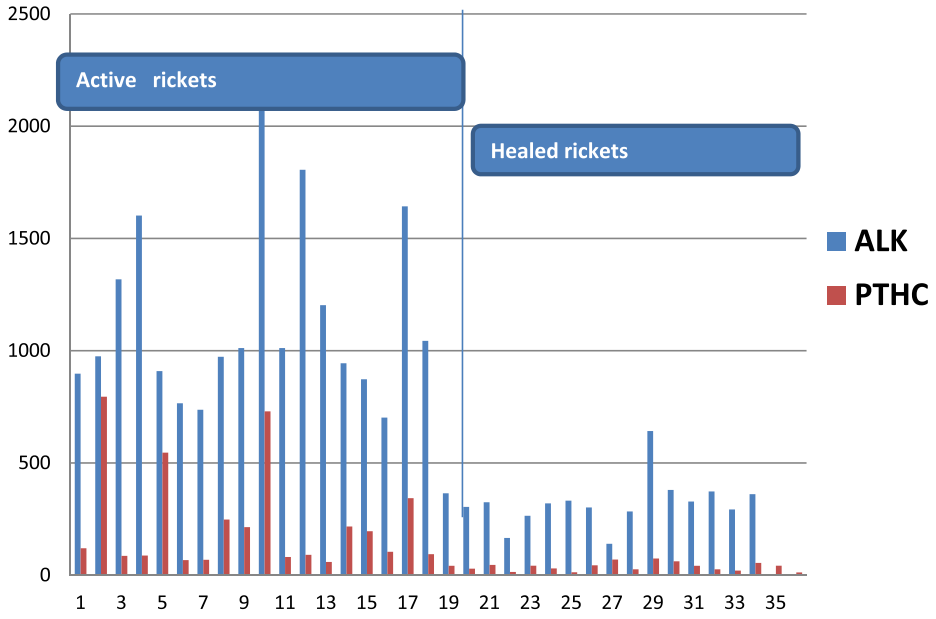

Figure 1: Parathormone (PTH) and Alkaline phosphatase (ALK) in active (left) healed (rt) rickets.

health problem. This is consistent with reports from other parts of Kingdom of Saudi Arabia.[1–5] The majority of the children were breastfed flat dwellers; they were mainly Saudis with a few from neighboring countries and only 6% of African origin. As a consanguinity rate of 66.1% is similar to that in other parts of Kingdom of Saudi Arabia, there is no evidence that genetic factors contribute to the incidence of the disease in the country.[14] Maternal educational level and paternal income were relatively high and cannot be associated with the development of rickets in this community. As the housing of the families was mainly flats (70%), lack of exposure to the sun plays a major part, as observed in previous studies.[1–6] This study further confirms that living in a flat with no exposure to sunlight is a major factor in the pathogenesis of rickets; therefore, play areas for children should be encouraged in residential areas.

The clinical features of rickets shown in Table 1 were divided into three groups to indicate the importance of early diagnosis of rickets for preventing the three serious associations and complications, convulsions, myelofibrosis and cardiomyopathy, and to avoid bone deformity.[4,5,14–18] One third of infants under 1 year presented with convulsions and the remainder with respiratory and gastrointestinal symptoms. General symptoms such as gastrointestinal and respiratory conditions continued to be seen in 1–2-year-old children but not in those over 2 years. Hypocalcaemic convulsions remain the commonest presentation of rickets during the first year of life in our and other studies, because hypocalcaemia is the first response to vitamin D deficiency.[4,5,14] Convulsions were not seen in children over 2 years of age because the calcium level was corrected by hyperparathyroidism, which moves calcium from the bones to the circulation. Such correction of calcium is vital for preventing serious complications.

The classical bone features of rickets, like waddling gait and limb deformities such as bow legs, knock knees and waddling gait, were seen after the children started to walk late in the second year of life. Deficiency occurring months before rickets is seen on physical examination; however, although growth failure, lethargy and irritability may be early signs of vitamin D deficiency, they are difficult to pinpoint. Wide wrist was the commonest sign in all three age groups, the rate varying between 88% and 93%. Costo-chondral beading was also present in the three groups, at 37% and 63%, as the ribs are the bones that grow fastest in the first year of life. The features of rickets depend on the rate of growth of each bone at the growing ends. When there is irregularity in the process of growth due to low calcium and phosphorus or secondary to vitamin D deficiency, all the growing ends show the abnormalities that characterize rickets, regardless of the cause. Frontal bossing was an obvious feature, occurring in 74% of children over 2 years and 89% of those aged 1–2 years, when the skull is the fastest growing bone. Waddling gait and bow legs are the most common cause of concern to parents after their child starts to walk, although delayed walking is one of the presenting features. In only one study were the features of rickets in children below 1 year of age compared with those over 1 year, which showed that the classical clinical features are not apparent during the first year of life, which is why rickets is underdiagnosed in this age group.[19] This is similar to what we observed in this study.

In the early phase of rickets, during the first year of life, the most important feature is 'biochemical rickets', namely hypocalcaemia and high alkaline phosphatase. The hypocalcaemia is attributable to the increased metabolic demands of rapid growth during these early age periods, resulting in symptomatic hypocalcaemia before any radiological changes occur.[14,20] If left untreated, these patients may later present with classical rickets.[14] We found high alkaline phosphatase in all cases of radiologically active rickets, regardless of the level of calcium or age, which decreased rapidly with radiological evidence of healing. Therefore, alkaline phosphatase could be used as an easily available screening test for rickets and vitamin D deficiency, and its decrease could be used as early evidence of healing.

The high incidence of respiratory symptoms can be related to the role of vitamin D in immunity. It was reported recently that cord blood levels of 25OHD are inversely associated with the risk for respiratory tract infections and childhood wheezing but not with the incidence of asthma.[21]

Prevention and Conclusion

We can conclude from this study that vitamin D deficiency rickets is still seen in Al-Medina region among breast fed infants heralded by maternal vitamin D deficiency in mothers as we have reported previously.[7] There is a report from Denmark showing that mothers with low vitamin D give birth to children with low vitamin D and increased risk of rickets. There are reports showing increasing rates of rickets due to insufficient sunlight exposure and inadequate vitamin D intake.[22,23] It is evident from recent studies that vitamin D deficiency has become a global problem being reported from snowy as well as sunny countries. Lowdon stated that exposure to the sun has a number of benefits. For example, it increases people's sense of wellbeing, allows them to synthesize vitamin D and provides opportunities for physical activity. A tendency for children to stay indoors and watch TV or play on computer games, rather than play outside when the sun is shining, is arguably also another contributing factor.[23] The American academy of pediatrics, now recommended that all infants and children, including adolescents, have a minimum daily intake of 400 IU of vitamin D beginning soon after birth. These revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D per day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer.[24] Also a Turkish nationwide 'vitamin D prophylaxis augmentation programme' initiated in 2005 reduced the prevalence of rickets from 6% in 1998 to 0.1% in 2008 in children under 3 years of age. The program included free distribution of vitamin D drops to all newborns and infants (0–12 months) visiting primary health stations throughout the country. Free disposal of vitamin D to infants is an effective strategy for preventing vitamin D-deficient rickets.[25] Further there is evidence of increased prevalence of CS in vitamin D deficient mothers.[26]

Saadi et al., assigned healthy breast feeding mothers to 2000 IU daily (group 1) or 60,000 IU monthly (group 2) of vitamin D(2), and all their infants received 400 IU daily of vitamin D for 3 months. Most infants had vitamin D deficiency - 25-hydroxyvitamin D [25(OH)D] $\leqslant$ 37.5 nmol/L- at study entry. Serum 25(OH)D concentrations at 3 months increased significantly. Maternal and infant serum 25(OH)D concentrations correlated positively at baseline and 3 months. Breast milk antirachitic activity increased from undetectable ($<$20 IU/L) to a median of 50.9 IU/L. They concluded that, combined maternal and infant vitamin D supplementation was associated with a threefold increase in infants' serum 25(OH)D concentrations and a 64% reduction in the prevalence of vitamin D deficiency without causing hypervitaminosis D.[27] Finally I would like conclude by a statement of Holick that, epidemiologic evidence and prospective studies have linked vitamin D deficiency with increased risk of many chronic diseases including autoimmune diseases, cardiovascular disease, deadly cancers, type II diabetes and infectious diseases. Vitamin D deficiency and insufficiency have been defined as a 25-hydroxyvitamin D $<$20 ng/ml and 21–29 ng/ml respectively. For every 100 IU of vitamin D ingested the blood level of 25-hydroxyvitamin D, the measured vitamin D status, increases by 1 ng/ml. It is estimated that children need at least 400–800 units IU of vitamin D a day while teenagers and adults need at least 2000 IU of vitamin D a day to satisfy their body's vitamin D requirement. It is estimated that 1 billion people worldwide are vitamin D deficient or insufficient. Correcting and preventing this deficiency could have an enormous impact on reducing health costs worldwide.[28] Depending on all these data we are suggesting measures of prevention of vitamin D deficiency and insufficiency by supplementing breast fed infants with 400 units of vitamin D3 daily from birth to two years. Maternal supplementation during pregnancy and lactation is also highly suggested and recommended by giving 1000 to 2000 units daily, from the second trimester, during pregnancy. This sort of program can be easily applied through Ministry of Health primary care centers for pregnant mother and their breastfed infants.

References

1. Elidrissy ATH, Taha SA. Rickets in Riyadh. In: Proceedings of 5th Saudi Med Meeting. 1980. pp. 409–418.
2. Fida NM. Assessment of nutritional rickets in Western Saudi Arabia. **Saudi Med J 2003**; 24(4): 337–340.
3. Al-Jurayyan NA, El-Desouki ME, Al-Herbish AS, Al-Mazyad MM, Al-Qhtani MM. Nutritional rickets and osteomalacia in school children and adolescents. **Saudi Med J 2002**; 23(2): 182–185.
4. Al-Atawi MS, Al-Alwan IA, Al-Mutair AN, Tamim HM, Al-Jurayyan NA. Epidemiology of nutritional rickets in children. **Saudi J Kidney Dis Transpl 2009**; 20(2): 260–265.
5. AlMustafa ZH, Al-Madan M, Al-Majid HJ, Al-Muslem S, Al-Ateeq S, Al-Ali AK. Vitamin D deficiency and ricl-Mustafkets in the Eastern Province of Saudi Arabia. **Ann Trop Pediatr 2007**; 27(1): 63–67.
6. Sedrani S, Alarabi K, Abannamy A, Elidrissy ATH. Book study of vitamin D status and factors to its deficiency in Saudi Arabia 1989. King AbdelAziz Center for Science and Technology (KACST).
7. Elidrissy ATH, Sedrani S, Lawson DEM. Vitamin D deficiency in mothers of rachitic infants. **Calcified Tissue Int 1984**; 36: 266–268.
8. Serinius F, Elidrissy ATH, Dandona P. Vitamin D nutrition in women at term, and in newly born babies in Saudi Arabia. **J Clin Pathol 1984**; 37: 444–447.
9. Belton NR, Elidrissy ATH, Forfar TB, et al.. Maternal vitamin D deficiency as a factor in the pathogenesis of rickets in Saudi Arabia. In: Normal AW, editor. *Biochemical and clinical endocrinology of calcium metabolism*. New York: Walter de Gruyter; 1982. p. 735–737.
10. Elidrissy ATH, Serinius F, Swailem AR. Perinatal vitamin D and its relation to infantile rickets. (Abstract) Symposium clinical disorders of calcium metabolism. Detroit, Michigan: 1983.
11. Taha SA, Dost SM, Sedrani SH. 25-Hydroxyvitamin D and total calcium extraordinary low plasma concentration in Saudi mothers and their neoantes. **Pediatr Res 1984**; 18: 739–741.
12. Thacher TD, Fischer PR, Pettifor JM, et al.. Radiographic scoring method for the assessment of the severity of nutritional rickets. **J Trop Pediatr 2000**; 46(3): 132–139.
13. Swailem AR, Serenius F, Edressee AW, et al.. Perinatal mortality in a Saudi maternity hospital. **Acta Pediatr Scand 1988**; 346: 57–69.
14. Ladhani S, Srinivasan L, Buchanan C, et al.. Presentation of vitamin D deficiency. **Arch Dis Child 2004**; 89(8): 781–784.
15. Cooperberg AA, Singer OP. Reversible myelofibrosis due to vitamin D deficiency rickets. **Can Med Assoc J 1966**; 94(8): 392–395.
16. Kamien B, Harris L. Twin troubles rickets causing myelofibrosis. **J Pediatr Child Health 2007**; 43(7–8): 573–575.

17. Verma S, Khadwal A, Chopra K, et al.. Hypocalcaemic nutritional rickets: a curable cause of dilated cardiomyopathy. **J Trop Pediatr 2011**; 57(2): 126–128.
18. Kim BG, Chang SK, Kim SM, et al.. Dilated cardiomyopathy in a 2 month old infant a severe form of hypocalcemia with vitamin D deficient rickets. **Korean Circ J 2010**; 40(4): 201–203.
19. Peng Lynn F, Serwint Janet RA. Comparison of breastfed children with nutritional rickets who present during and after the first year of life. **Clin Pediatr Rev 2003**; 42: 711–717.
20. Elidrissy ATH. Pathogenesis of rickets in a sunny country. In: Glorieux FH, editor. Rickets 1991. Vevey: Nestlé/New York: Raven Press; pp. 123–143.
21. Carlos A, Camargo JR, Ingham T, Wickens K, et al.. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing and asthma. **Pediatrics 2011**; 127: 180–187.
22. Mølgaard C, Michelson KF. Vitamin D and bone health in early life. **Proc Nutr Soc 2003**; 62(4): 823–828.
23. Lowdon J. Rickets: concerns over the worldwide increase. **J Fam Health Care 2011**; 21(2): 25–29.
24. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. **Pediatrics 2008**; 122(5): 1142–1152.
25. Hatun Ş, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. **Acta Pediatr 2011**; 100(9): 1195–1199.
26. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. **J Clin Endocrinol Metab 2009**; 94(3): 940–945.
27. Saadi HF, Dawodu A, Afandi B, Zayed R, Benedict S, Nagelkerke N, Hollis BW. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. **Matern Child Nutr 2009**; 5(1): 25–32.
28. Holick MF. Vitamin D: evolutionary, physiological and health perspectives. **Curr Drug Targets 2011**; 12(1): 4–18.